

FORM-3A

THE PATENTS ACT, 1970

COMPLETE

Specification

SECTION 10

The following Specification Particularly describes
and ascertains the nature of this invention and the manner
in which it is to be performed.

Present invention relates to a process for preparation of urea complexes of Vitamin E and it's esters. Nonadductible vitamin E and it's esters can easily be included in urea by this process. Vitamin E, a thick viscous liquid can be included in urea in the presence of rapidly adductible endocyt to yield crystals of urea complexes of Vitamin E with improved handling characteristics and stability.

Vitamin E whether natural or synthetic and whether in the form of alcohol or ester is highly unstable and susceptible to deterioration upon exposure to air, light and heat. Despite extensive research during past few decades, the stability of vitamin E still remains a challenge for scientific community.

Some success in stabilization of vitamin E preparations has been achieved here-to-fore by various techniques. In one such technique suitable antioxidant/s is/are incorporated in the formulation to minimize oxidation of vitamin E. Antioxidants such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) have been used for the stabilization of vitamin E or its esters. Although the use of antioxidants protects the vitamin E against oxidation but does not altogether prevents its decomposition which can be via photolytic route. Although tocopherol is used as an antioxidant itself so as to stabilize various other drugs prone to oxidation which it undergoes over other oxidisable moieties. Therefore selection of a suitable antioxidant for such a drug still remains a problem.

Since the decomposition of vitamin E is catalyzed by metallic ions, therefore, the use of sequestering agents such as EDTA (ethylene diamine tetraacetic acid) and disodium EDTA has also being reported for enhancement of stability of vitamin E and its esters. Here also the adverse influence of light in the degradation of vitamin E remains untouched.

Protective coatings are being widely utilized to prevent exposure of vitamin E and its esters to atmospheric oxygen and light. Wide range of materials of diverse nature have been employed for encapsulation of Vitamin E and its esters. Various coating techniques being employed are not only expensive but even the resulting coatings are susceptible to various defects such as poor core-coat adhesion, discontinuity in coating, nonuniformity of coating and various other coating defects.

Another technique for stabilization of vitamin E and its esters involves preparation of inclusion compounds with deoxycholic acid (DCA) and apocholic acid. Improved stability with regard to oxidising agents, air, light and heat alongwith enhanced utilization by animals was claimed. However the high cost of bile acids limits the use of this technique.

In present invention complexes of urea with vitamin E and it's esters such as vitamin E acetate have been prepared. These are novel complex compounds of vitamin E or it's esters and rapidly adductible endocyt with urea. Urea does

not form inclusion compound with vitamin E and its esters under any known conditions. Under normal conditions urea forms adducts with all straight chain compounds above a certain minimum length. It forms adducts with hexane or longer compound in case of normal alkanes, hexene or longer in case of normal alkenes, acetone or longer in case of straight chain ketones and butyric acid or longer in case of straight chain acids. The channel in the hexagonal urea unit cell varies from 5 to 6 angstroms in diameter. Normal paraffin molecules being about 4.1 Angstroms in diameter readily form adducts with urea. Highly branched molecules such as those of 2,2, 4-trimethyl pentane are of the order of 6 Angstroms diameter and consequently does not form adduct with urea under any known conditions. Molecules between these sizes may form adducts with urea in certain cases and not form in others. For example, benzene molecules are about 5.9 Angstroms in the largest dimension. Benzene does not form an adduct with urea but 1-phenyloctadecane does. The long straight chain of this compound is readily adducted and apparently unit cell can withstand occasional distortion caused by benzene molecules.

Vitamin E and its esters are highly substituted and are not known to form adducts with urea under any known conditions. In the present invention, nonadductible vitamin E and its esters can be easily included in urea in the presence of suitable rapidly adductible endocycle. Number of long straight chain compounds such as fatty acids, alkanes, alkenes, alcohols, amino acids, monoesters, diesters can be employed as rapidly adductible endocycles. Stearic acid, palmitic acid, linoleic acid, n-octane and n-octanol represent some of the rapidly adductible endocycles. Vitamin E or its esters can be included in urea by the present invention.

General Procedure : Urea and suitable rapidly adductible endocycle (i.e. straight chain compound such as palmitic acid, stearic acid and linoleic acid) can be dissolved in any suitable solvent/s such as methanol by heating. After solubilization has been effected, vitamin E or any suitable ester of vitamin E such as vitamin E acetate can be incorporated and the resultant mixture heated till complete dissolution occurs. The solution is allowed to cool to room temperature. Crystals of urea complexes comprising of urea, vitamin E or its ester rapidly adductible endocycle will separate out which can be separated from mother liquor and dried under vacuum. The entire operation can be optionally conducted under subdued light in an atmosphere of inert gas.

The general process for preparation of urea based complexes of vitamin E or its ester has been diagrammatically illustrated in Figure 1 of the accompanying drawing.

This process is exemplified but not limited by the following :-

Example 1 : Add 2 g of vitamin E and 2 g of stearic acid to 40 ml of methanolic solution containing 20 g of urea. Heat resultant mixture till complete solubilization occurs. Allow this solution to cool when formation of crystals of urea complexes containing vitamin E and stearic acid can be observed. Resulting magma can be allowed to remain at room temperature for about 2-3 hours. Separate the crystals of urea complexes from mother liquor and dry under vacuum. Conduct the entire procedure optionally under subdued light and in an atmosphere of nitrogen or any other suitable inert gas.

Example 2 : Add 1 g of vitamin E, 1.4 g of linoleic acid and 12.5g of urea to 25-75 ml of methanol. Heat the resultant mixture till complete solubilization. Cool this solution to allow formation of crystals of urea complexes containing vitamin E and linoleic acid. Allow resultant magma to remain at room temperature for 2-3 hours with occasional agitation. Separate the crystals of urea complexes from mother liquor and dry under vacuum. Perform the entire experiment optionally under subdued light and in an atmosphere of nitrogen gas.

Vitamin E esters can also be similarly included in urea.

We Claim :

1. A process for preparation of urea complexes of vitamin E and it's esters which comprises of solubilising vitamin E or it's ester of the kind such as herein described, rapidly adductible endocyte of kind such as herein described and urea in suitable solvent such as methanol by heating till complete dissolution, cooling the resultant solution with optional agitation to allow urea complexes containing vitamin E or its ester to crystallise, separating the resulting crystals from mother liquor by known methods and subsequently drying these crystals to yield urea complexes containing vitamin E or it's ester.
2. A process as claimed in claim-1, substantially as herein described and exemplified in examples 1 and 2.

Dated, this 24th day of October, 1994.


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No. of Sheets : 1
Sheet No. : 1

Application No. 1340/DEL/94

Suitable rapidly adductible
Endocyte (RAE)

Solvent make up

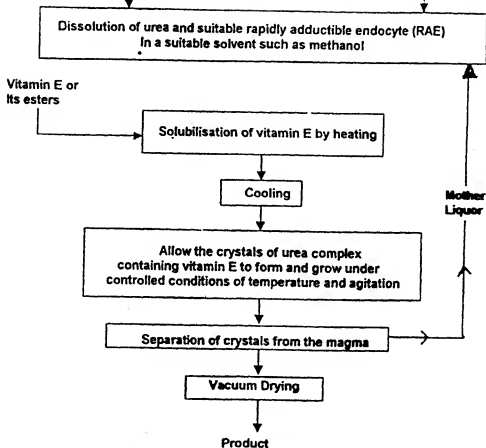


Figure 1 : Flowchart of preparation of urea complexes of Vitamin E and its esters.

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